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REVIEW

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Unlocking the power of precision medicine: exploring the role of biomarkers in cancer management

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Abstract

Background Personalized or Precision medicine (PM) is a promising approach for the cancer treatment that tailors treatment to a patient's characteristics. Biomarkers are crucial for identifying the patients who are expected to derive greatest advantage from targeted therapy.

Main body Here, various biomarkers, including genetic, epigenetic, protein, and metabolites, and their clinical significance, are discussed. The review provides insights into the use of biomarkers and their clinical significance in cancer treatment. There are several hurdles in use of PM in oncology, such as the complexity of tumor biology and heterogeneity, limited availability of biomarkers, high cost of targeted therapies, resistance to targeted therapies, and ethical and social issues.

Conclusion The biomarkers play a crucial diagnostic role in the treatment of cancer. The review also acknowledges the challenges and limitations of personalized medicine which, if resolved, can be helpful in the management of cancer.

Keywords Personalized medicine, Biomarkers, Cancers, Genetics, Oncogenes

Background

The old concept "One size fit for all" is now turned into an individualized tailormade approach to personalized or precision medicine (PM). Cancer is a complex and heterogeneous disease that is responsible for a significant proportion of morbidity and mortality worldwide. Despite decades of research, the management of cancer remains a significant challenge due to the diverse biological and genetic characteristics of tumors. Since it is based on the distinct molecular characteristics of each patient's tumor, PM has revolutionized cancer treatment. PM has shown promise in improving treatment outcomes and reducing toxicities associated with traditional chemotherapy. As PM continues to evolve, more effective and targeted therapies will likely emerge in near future, offering hope for patients with previously incurable cancers [1].

National Human Genome Research Institute, U.S. has defined PM as, "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made regarding the prevention, diagnosis, and treatment of disease." It is a medical model that considers individual patients characteristics, including genetic, environmental, as well as lifestyle [2]. PM is particularly important because cancer is a complex disease that can vary significantly from individual to individual. What works for one patient may not work for another, and what causes cancer in one person may not be the same as what causes it in another [3]. Figure 1 depicts points which give a brief idea of why PM is important.

PM is an approach to medical treatment that considers the individual patients' medical needs. To examine

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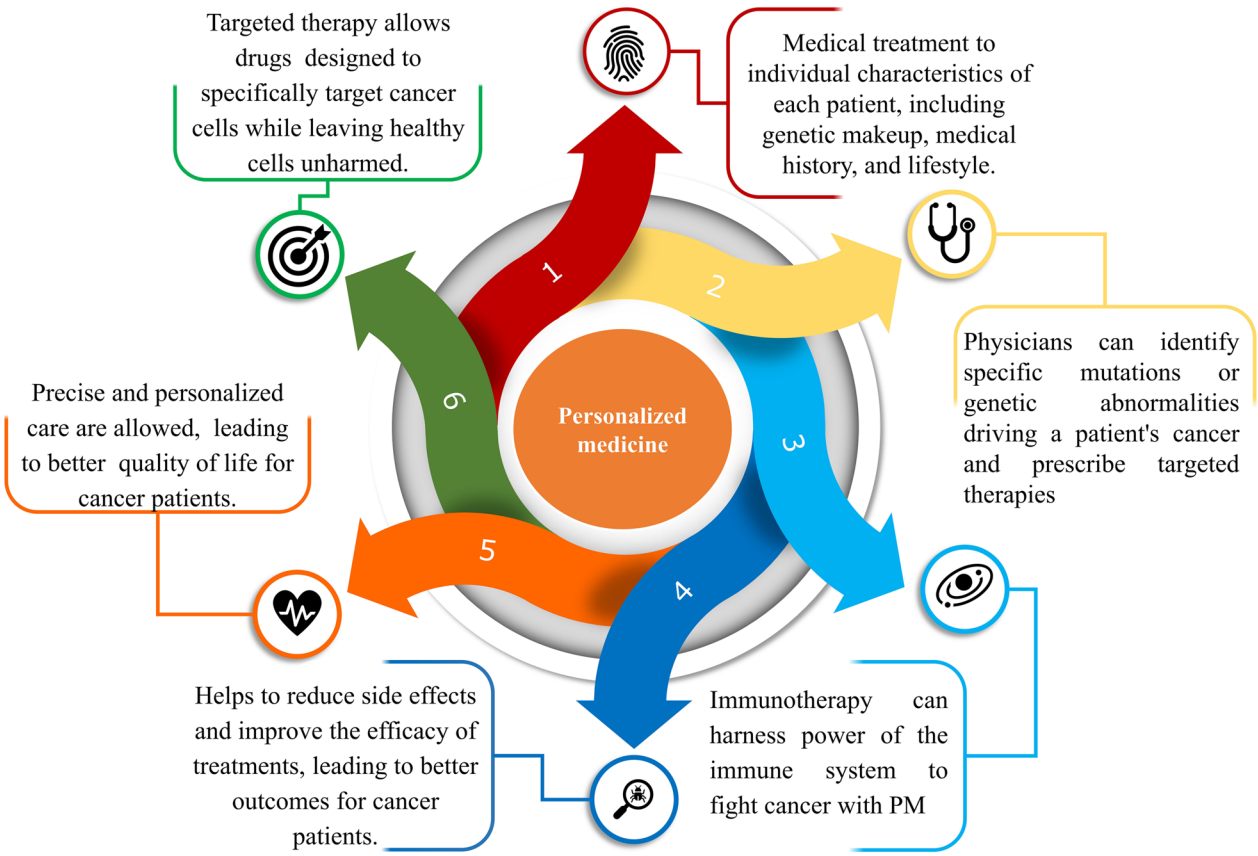

Fig. 1 Characteristics of PM

the distinct genetic and molecular characteristics of each patient's cancer, the method makes use of a variety of technologies and instruments. The PM approach in oncology involves collaborative efforts among healthcare workers including physicians, radiation oncologists, surgeons, nursing staff, pharmacists, etc. This team works together to gather all the necessary information about the patient's cancer and with the use of that information to design a personalized treatment plan [4].

Main text

Definition of biomarkers and their role in oncology

Biomarkers are defined as, "measurable indicators of normal or abnormal biological processes, and they can be used to diagnose diseases, monitor disease progression, and guide treatment decisions." In oncology, biomarkers can also be used to identify subtypes of cancer that may have different treatment requirements. A well-known example is breast cancer which can be classified into different subtypes based on the presence or absence of certain biomarkers, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This information can be used to guide treatment decisions, such as whether to use hormone therapy or chemotherapy [5]. The biomarker test is also referred to as 'liquid biopsy'. Biomarkers are molecules that can be found in blood, tissue, or other bodily fluids that can indicate the presence or severity of a particular disease [6].

Targeted therapy, on the other hand, is a type of cancer treatment that specifically targets cancer cells, while sparing healthy cells. Biomarkers play a critical role in the development of targeted therapies by identifying the specific molecular targets that are involved in cancer growth and progression [7]. The growing interest in the use of biomarkers in PM is revealed in PubMed database Search shown in Fig. 2. Using these tools to identify the specific molecular pathways that are involved in cancer growth and progression, researchers and doctors can develop more effective and targeted treatments for patients with cancer. As we continue to learn more about cancer and its underlying causes, biomarkers and targeted therapy will become even more important in the fight against this devastating disease [8].

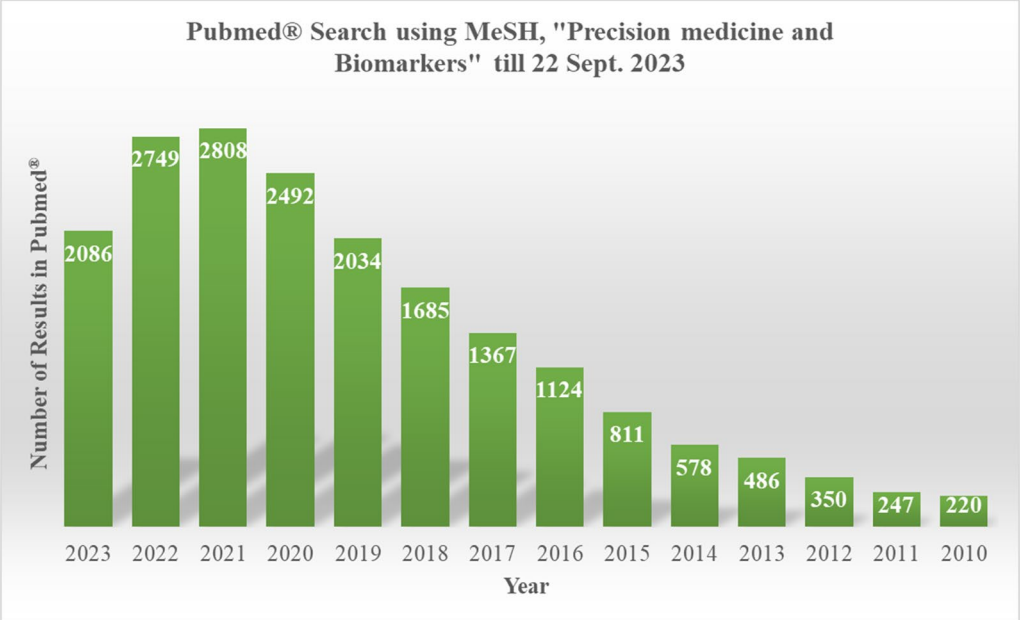

Fig. 2 Pubmed® Search using MeSH, "Precision medicine and Biomarkers" (till 22 Sept. 2023)

Different types of biomarkers

There are several different types of biomarkers which include genetic biomarkers, epigenetic biomarkers, metabolite biomarkers and protein biomarkers. Once a biomarker has been identified, researchers can use that information to develop therapies that specifically attack the molecular pathways that are involved in cancer growth and progression [9]. Several different types of biomarkers that can be used in medicine, each with its usage and examples shown in Table 1.

Genetic biomarkers

Genetic mutations or other genetic abnormalities that are specific to certain diseases. Genetic biomarkers can serve as a clinical guide for treatment selection customized for the patients. Patients with certain genetic mutations may benefit from targeted therapies that specifically target the molecular pathways that are involved in cancer.

There are several types of genetic biomarkers for cancer, including:

Oncogenes Oncogenes are genes that can cause cancer when they are overactive or mutated and are depicted in Fig. 3. Proto-oncogenes are normal genes that allow cells growth and division or allow them to thrive [10]. However, when a proto-oncogene undergoes a mutation, it can become an oncogene, which is activated when it should not be. Oncogenes are like gas pedals that are stuck down, causing cells to divide uncontrollably, leading to the development of cancer. Different factors such as gene variants, epigenetic changes, chromosome rearrangements, and gene duplication can turn on oncogenes in cells. These factors cause changes in the DNA or RNA sequence, chemical groups attached to genetic material, or extra copies of a gene, leading to the production of too much protein that drives uncontrolled cell growth. Eg. HER2, BRAF, c-KIT, NF1 and KRAS [10].

Tumor suppressor genes Tumor suppressor genes are those genes that normally help to prevent cancer by regulating cell growth and division. The mutated genes lead to cancer as shown in Fig. 4. Tumor suppressor genes act as brake pedals in cells, slowing down cell division to prevent excessive growth. The deactivation of tumor suppressor genes can cause carcinogenesis. While the majority of mutations are acquired, some types of cancer are passed down through families due to abnormalities in tumor suppressor genes. More than 50% of all cancers are caused by mutations in the TP53 gene, which makes the p53 protein. These mutations can occur in many different types of cancer. Other such genes includes TP53, BRCA1, and BRCA2, etc. [11].

DNA repair genes DNA repair genes are involved in repairing DNA damage that can lead to cancer. Mutations in these genes can increase the risk of developing cancer. During cell division, errors may occur while copying the DNA, and DNA repair genes help to identify and repair these mistakes or trigger cell death if they can't be fixed. When DNA repair genes don't function properly, mistakes can accumulate, which may lead to uncontrolled cell growth. Changes in DNA repair genes

Table 1 Biomarkers used in cancer

Type of biomarker	Description	Usage	Examples
Genetic biomarkers	Mutations or other genetic abnormalities specific to certain diseases	Identifying patients who are more likely to respond to targeted therapies for cancer, such as the EGFR (epidermal growth factor receptor) mutation in lung cancer	MutL protein homolog 1 (MLH1), MutS homolog 2/6 (MSH2/6), PMS1 homolog 2 (PMS1/2), Breast cancer type ½ (BRCA1/2), Kirsten rat sarcoma viral oncogene homolo (KRAS), Tumor protein p53 (TP53), etc.
Epigenetic biomarkers	Changes in gene expression associated with disease	Diagnosing and treating cancer, such as the DNA methylation in breast, lung and colon cancer	Histone modification, Non-coding RNAs, Chromatin accessibility, MicroRNA expression
Protein biomarkers	Proteins produced by disease cells that can be detected in the blood or tissue of patients	Monitoring the progression of cancer	C-reactive protein (CRP), Troponin, Cancer antigen 125 (CA-125), HER2, B-type natriuretic peptide (BNP)
Metabolite biomarkers	Produced during metabolism and associated with tumor growth	Used as a biomarker for the diagnosis and monitoring of lung, pancreatic, thyroid, breast and hepatic cancer	Palmitic acid, Cholesterol, Lactate, Creatinine, Triglycerides, Urea, Ketone bodies
Transcriptome biomarkers	Changes in the expression of RNA molecules that are indicative of cancer	Differentiate types of cancers, Identify molecular targets for cancer	Immune-related genes (CD8A, IFNG), Non-coding RNA molecules (microRNAs, long non-coding RNAs-), Splice variants of RNA

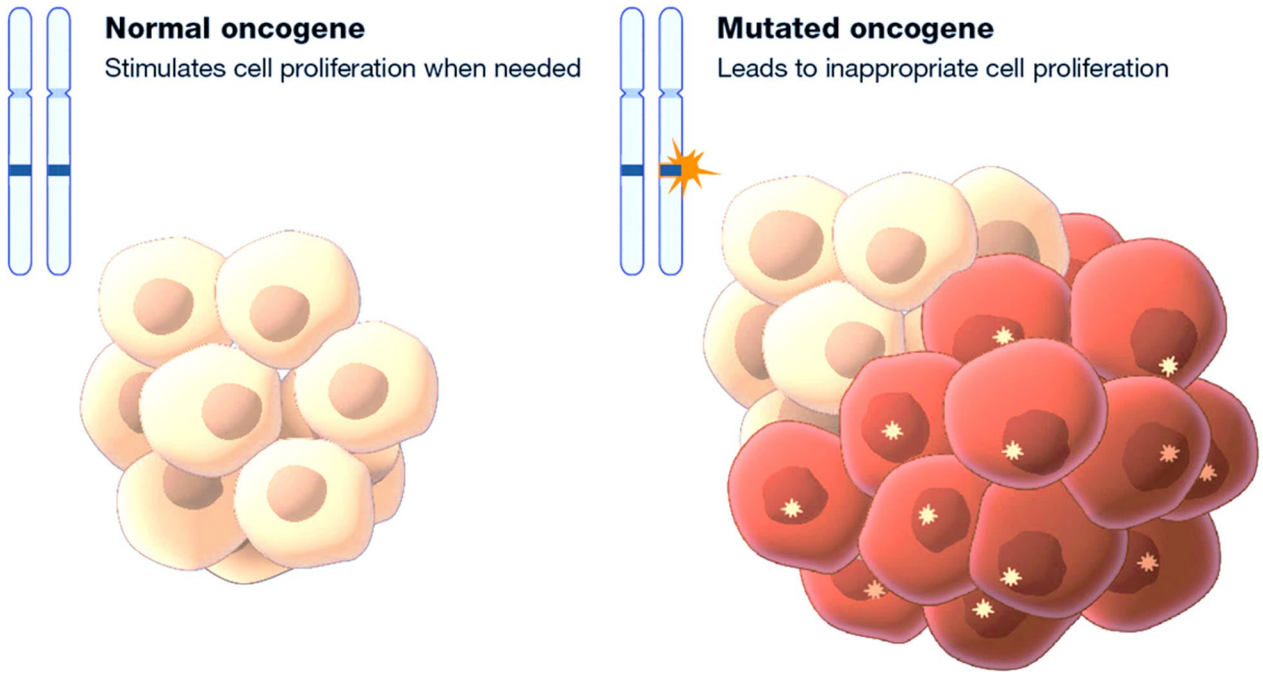

Fig. 3 Normal and mutated Oncogenes (Courtesy-National Human Genome Research Institute https://www.genome.gov/)

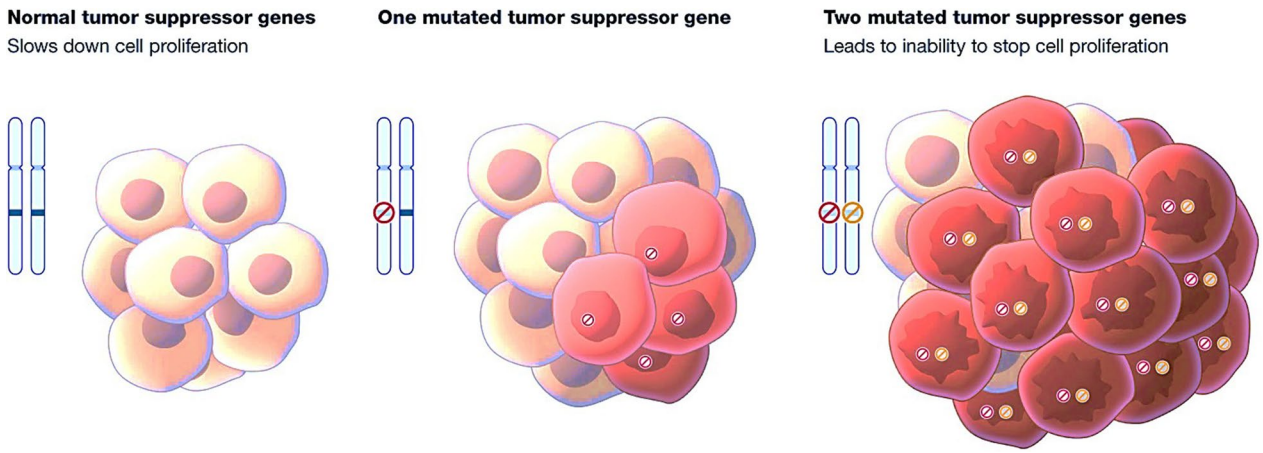

Fig. 4 Normal and mutated tumor suppressor genes (Courtesy-National Human Genome Research Institute https://www.genome.gov/)

can be inherited or acquired, just like other types of gene mutations. The BRCA1 and BRCA2 genes are examples of DNA repair genes that, when mutated, increase the risk of certain cancers, especially breast and ovarian cancer. However, mutations in these genes can also occur in tumor cells of individuals who did not inherit them. Eg. MSH2 and MLH1 [10].

Microsatellite instability (MSI) MSI is a biomarker that indicates a defect in a short segment of DNA leading to an increased risk of cancer development. MSI are prone to errors during DNA replication and repair. MSI is commonly seen in certain types of cancer, such as colorectal, gastric, breast, thyroid, and prostate cancers, cholangiocarcinoma, leukaemia, endometrial carcinoma, pancreatic ductal adenocarcinoma, etc. It can be further classified as MSI-low and MSI-high. However, currently, MSI-low and microsatellite stability are considered the same. Further details are reviewed by Baudrin et al. [12] and Li et al. [13] MSI can be detected using next generation sequencing, immunohistochemistry and single molecule inversion probes having accuracy more than 90%. However, fluorescent multiplex polymerase chain

reaction and capillary electrophoresis are referred as gold standard for MSI detection having accuracy 100%. Fluruouracil, nivolumab, ipilimumab, pembrolizumab, and bevacizumab are reported to be useful in colorectal cancer with MSI [13].

Epigenetic biomarkers

Epigenetic biomarkers measures variation in disease or drug associated epigenic expressions that can also be used to identify disease. Epigenetic biomarkers are particularly useful in the diagnosis and treatment of cancer. The DNA molecules and the proteins that interact with DNA can undergo chemical modifications that influence the activation and deactivation of genes. These modifications can be passed on from one cell to another during cell division, and they can also be passed from one generation to the next. All epigenetic changes that occur in a genome are referred to as an epigenome [14]. Some epigenic biomarkers are discussed below.

DNA methylation

DNA methylation is a common epigenetic modification that involves the addition of a methyl group to DNA. Methylation of CpG islands, which are often located in the promoter regions of genes, can lead to gene silencing. Aberrant DNA methylation patterns have been observed in many types of cancer, including breast, lung, and colorectal cancer [15].

Histone modifications

Histone proteins, which package DNA in the nucleus, can be modified by the addition or removal of chemical groups. These modifications can alter the accessibility of DNA to the transcriptional machinery and can affect gene expression. For example, acetylation of histones is generally associated with gene activation, while deacetylation is associated with gene silencing. Changes in histone modifications have been observed in many types of cancer, including leukaemia, prostate, liver, and lung cancer [16, 17].

Protein biomarkers

These are other types of biomarkers that can be used in medicine. Protein biomarkers are specific proteins that are produced by disease cells and can be detected in the blood or tissue of patients with the disease. Protein biomarkers are particularly useful in the diagnosis and monitoring of cancer. Certain proteins such as PSA, CA-125, HER2, CEA, etc. may be overexpressed in cancer cells, and monitoring the levels of these proteins in the blood or tissue of patients can help a physician to track the progression of the disease [18].

Metabolite biomarkers

These are small molecules that are produced by cellular metabolism, and they can be detected in biological samples such as blood, urine, or tissue. Metabolite biomarkers could be a useful tool for the diagnosis of lung, pancreatic, thyroid, breast and hepatic cancer, etc. as they offer a non-invasive and cost-effective approach to disease detection. The diagnostic accuracy of metabolite biomarkers could be further improved by combining multiple biomarkers into a single diagnostic test [19].

Nucleotide metabolites

Nucleotide metabolites are involved in DNA synthesis and repair, and their levels can be altered in cancer cells. The increased levels of deoxythymidine monophosphate (dTMP) and decreased levels of inosine monophosphate (IMP) have been observed in breast cancer cells. Antimetabolites targeted toward Thymidylate synthase, Dihydrofolate reductase and Glycinamide ribonucleotide formyl transferase are used in clinical practice [20].

Amino acid metabolites

Amino acid metabolites are involved in protein synthesis and energy production, and their levels can be altered in cancer cells. The increased levels of alanine and decreased levels of glutamate have been observed in lung cancer cells. Higher levels of Kynurenine are observed in lung and ovary cancer while Hydroxyproline has been related to hepatic cancer [21].

Lipid metabolites

Lipid metabolites are involved in cell membrane structure and function, and their levels can be altered in cancer cells. Increased levels of phosphocholine and decreased levels of phosphatidylcholine have been observed in breast cancer cells. Targeting Stearoyl CoA-desaturase can benefit in gastric cancers and it is also associated with hepatic cell cancer. High levels of phospholipase A2 are associated with colorectal cancer [22].

Carbohydrate metabolites

Carbohydrate metabolites are involved in energy production and cell signaling, and their levels can be altered in cancer cells. The increased levels of lactate and decreased levels of glucose have been observed in many types of cancer cells. Glycoproteins antigens such as CA19-9, CA125, and α-fetoprotein are found to have diagnostic potential in colon carcinoma and ovarian cancer.

Iminosugars such as swainsonine, Castano spermine, siastatin B, etc. reported to exhibit antitumor effects [23].

Transcriptome biomarkers

It refers to the group of biomarkers that are identified based on changes in gene expression patterns. Transcriptome biomarkers can be used to understand disease progression, drug efficacy, and patient response to treatment. By analyzing the changes in gene expression between different conditions, researchers can identify specific genes or sets of genes that are upregulated or downregulated [24]. Two types of transcriptome biomarkers are discussed below.

mRNA expression biomarkers

The oncotype DX test measures the expression of twenty genes in breast cancer tissue and is used to envisage the recurrence and the possible benefit of chemotherapeutic treatment. *PAM50* test is used as a tool to check the expression of fifty genes and it serves to classify breast cancer based on prognosis and treatment outcomes. *Mammaprint* is another test that is used to check seventy genes expression in breast cancer tissue and is used to predict the risk of recurrence and the potential benefit of chemotherapy [25].

Decipher gene expression test measures the genetic expression in prostate tumor and serve as tool to identify recurrence and effects of radiation therapy. The test score as shown in Fig. 5 is useful in the prediction of risk of prostate cancer [26].

Non-coding RNA biomarkers

Non-coding micro-RNA biomarkers viz. *MiR-21, MiR-155* and long non-coding biomarkers HOTAIR, MALAT1, etc. are known to be upregulated in many types of cancer, including breast, lung, liver, and colorectal cancer. These are used as a tools to determine tumor progression invasion and metastasis [27, 28].

These biomarkers all have unique strengths and limitations, and can be used in different ways to diagnose, monitor, and treat a wide range of diseases. By identifying the specific biomarkers associated with a particular disease, doctors can develop more personalized treatment plans for their patients.

Imaging biomarkers (IB)

IB are integral part of routine cancer management serving as indispensable tool in the standard care of the cancer patients and clinical decision making. The key techniques used as IB are magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography scan and ultrasound imaging. These techniques provide information about patient health, diagnosis, disease progress and response to the treatment. The quantifiable characteristics including size, shape, density, texture, and functional information of the tumor allows the healthcare providers to tailor the treatment plans [29]. Artificial intelligence can be trained using a prior database of IB to redefine the biomedical imaging as a clinical decision making tool and to improve diagnostic precision [30, 31].

Spotlight on biomarkers in cancer

HER2 in breast cancer

HER2 protein is overexpressed in approximately 20% of breast cancers, and its overexpression is associated with a more aggressive form of the disease. HER2 plays a critical role in breast cancer development and progression. HER2 overexpression can lead to abnormal cell signaling, increased cell proliferation, and decreased apoptosis (programmed cell death). It all contribute to tumor growth and spread. HER2 has also been identified as a target for breast cancer treatment. Drugs that target HER2, such as trastuzumab and pertuzumab, have been shown to be effective in the treatment of HER2-positive breast cancer. Additionally, nelipepimut-S vaccine trastuzumab–emtansine conjugate is also strategically employed in clinical setting against HER2. However, it is worth to noting that trastuzumab–deruxtecan is known to cause hematological effects, hepatic toxicity and gastrointestinal toxicity. In some cases pulmonary toxicity with it caused death [32].

Furthermore, tyrosine kinase (TK) inhibitors designed to inhibit HER2 were also developed. Lapatinib and pyrotinib are reversible while neratinib and tucanib are

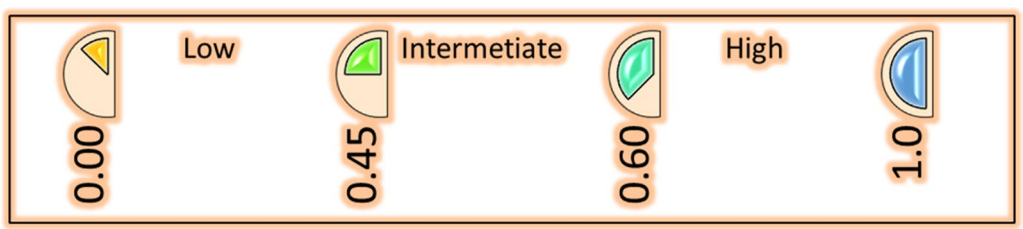

Fig. 5 Decipher scores and risk of metastasis and death from prostate cancer

irreversible TK inhibitors. These drugs can be prescribed for advanced breast cancer [33].

EGFR in non-small cell lung cancer (NSCLC)

EGFR mutations are present in approximately 10–15% of NSCLC cases, with the majority of these mutations being exon 19 deletions or exon 21 L858R substitutions. These mutations lead to the activation of the EGFR pathway, which plays a critical role in the development and progression of NSCLC. Targeted therapies that inhibit EGFR activity, such as gefitinib, erlotinib, and afatinib, have been developed and are effective in treating NSCLC patients with EGFR mutations. However, resistance to these drugs can develop over time, and alternative therapies are needed. Osimertinib is a third-generation EGFR inhibitor that is effective in treating NSCLC patients with EGFR mutations, including those with resistance to first-generation EGFR inhibitors. It may be a more effective than the first-line treatment option for NSCLC patients with EGFR mutations [34].

Raf murine sarcoma viral oncogene homolog B (BRAF) in melanoma

BRAF mutations are present in approximately 50% of melanoma cases and lead to the activation of the Mitogen-activated protein kinase (MAPK) signaling pathway, which plays a critical role in the development and progression of melanoma. BARF mutations can cause unstoppable cell division which may lead to tumor formation. BRAF V600E is a very commonly observed type of mutation where mutations occur in valine (V) and glutamic acid. It is useful as a prognostic marker in the detection of malignancies. BARF mutations are a reason for adenocarcinoma in nonsmoking as well as women population [35]. Its testing is suggested in metastatic colorectal cancer [36].

Targeted therapies that inhibit BRAF activity, such as vemurafenib, dabrafenib, and encorafenib, have been developed and are effective in treating melanoma patients with BRAF mutations. However, resistance to these drugs can develop over time, and alternative therapies are needed. In addition, targeted therapy can also lead to adverse events, such as skin toxicity and the development of secondary malignancies. The development of combination therapies that target multiple pathways, the use of immunotherapy to enhance the immune response to melanoma, and the identification of biomarkers that can predict response to targeted therapy and help guide treatment decisions. The identification of predictive biomarkers, such as baseline lactate dehydrogenase levels, can also help guide treatment decisions and improve patient outcomes [37].

BRCA1/2 mutations

BRCA1/2 are genes that are involved in DNA repair. Mutations in these genes increase the risk of developing breast and ovarian cancer. Testing for BRCA1/2 mutations can help identify individuals who are at high risk of developing these cancers and may benefit from early screening and preventive measures. Breast cancer that is associated with BRCA1/2 mutations may respond better to certain types of chemotherapy, such as platinum-based drugs. Additionally, some targeted therapies, such as poly ADP-ribose polymerase (PARP) inhibitors, have shown promise in treating breast and ovarian cancers that are associated with BRCA1/2 mutations. In cells with BRCA1/2 mutations, PARP inhibitors can lead to the accumulation of DNA damage and ultimately cell death. PARP inhibitors have been approved for the treatment of certain types of ovarian and breast cancers that are associated with BRCA1/2 mutations. PARB inhibitors olaparib, rucaparib, and niraparib are approved for cancer treatment [38, 39].

Clinical significance of biomarker-based PM

Biomarkers are measurable indicators of physiological or pathological processes, and their use in PM allows for tailored treatment strategies based on individual patient characteristics. The clinical significance of PM is summarized in Fig. 6. Biomarker-based PM has significant clinical significance in cancer treatment. Biomarkers help identify patients who are most likely to respond to specific therapies, enabling clinicians to select the most appropriate treatment for an individual patient. Biomarker-based PM can also help reduce the use of ineffective treatments, saving patients from unnecessary toxicity and healthcare costs. Biomarker-based PM can also help reduce the use of ineffective treatments, saving patients from unnecessary toxicity and healthcare costs. For example, testing for KRAS mutations in colorectal cancer can identify patients who will not benefit from anti-EGFR therapy such as cetuximab [40].

Screening

Biomarkers can be used in cancer screening to identify individuals who may be at increased risk of developing cancer. The elevated levels of PSA in the blood can be a sign of prostate cancer and may prompt further testing. Other biomarkers, such as carcinoembryonic antigen (CEA), can be used to monitor the response to treatment in patients with certain types of cancer [41]. It is reported that Circulating tumor DNA (ctDNA) such as EGFR, KRAS or BRAF and protein biomarkers like CA125, CEA, etc. in addition to screening may be helpful in monitoring response in lung cancer patients [42].

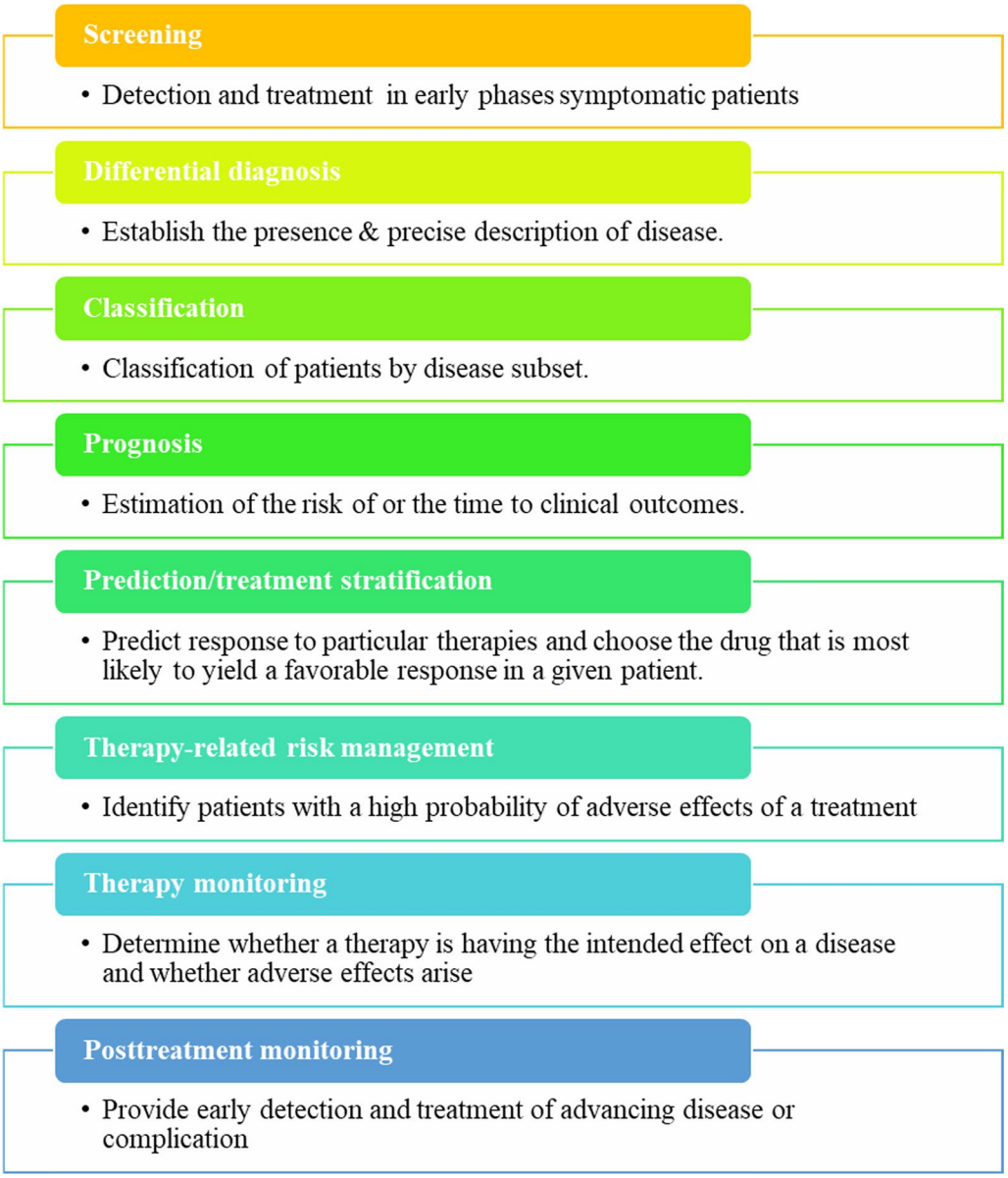

Fig. 6 Clinical significance of biomarkers at different stages of cancer

Differential diagnosis

Liquid biopsy can help distinguish between different types of cancer or between cancer and non-cancerous conditions. Testing for the presence of specific gene mutations, such as EGFR mutations in lung cancer, can help determine the appropriate treatment for the patient. Elevated levels of PSA in the blood can be a sign of prostate cancer, but can also be elevated in non-cancerous conditions such as benign prostatic hyperplasia (BPH) or prostatitis. CA-125 is often used as a biomarker for ovarian cancer, but it can also be elevated in other conditions such as endometriosis or fibroids. CEA can be elevated in a variety of cancers, including colon, lung, and pancreatic cancer, but can also be elevated in non-cancerous conditions. ALK gene rearrangements are commonly found in NSCLC, but can also be present in other types of cancer, such as anaplastic large-cell lymphoma [43, 44].

Cancer classification

Biomarkers can also be used to classify different types of cancer based on their molecular characteristics. Breast cancer can be classified into different subtypes based on the expression of certain genes, such as ER and HER2. This information can be used to guide treatment

decisions and predict the response to therapy. BRAF mutations are used to classify melanoma as either BRAF-mutant or BRAF-wildtype. MSI is used to classify colorectal cancer as either MSI-high or MSI-low/microsatellite stable [45].

Prognosis

Biomarkers can provide important information about the likely course of the disease and the patient's chances of survival. Testing for the expression of certain genes, such as the Oncotype DX gene panel in breast cancer, can help predict the likelihood of cancer recurrence and guide treatment decisions. Ki-67 is a protein that is present in rapidly dividing cells and is commonly used as a biomarker of tumor proliferation. High levels of Ki-67 expression and mutations in the p53 gene are associated with poorer outcomes in breast cancer, lung cancer, and other types of cancer [46].

Cancer prediction and treatment stratification

Biomarkers can be used to predict the likelihood of developing cancer or to stratify patients into different treatment groups based on their risk profile. Genetic testing for mutations in the BRCA1/2 genes can help identify individuals who are at increased risk of developing breast and ovarian cancer and may benefit from more frequent screening or prophylactic surgery. BCR-ABL gene fusion is associated with chronic myelogenous leukemia (CML) and can be targeted with tyrosine kinase inhibitor therapy, which has dramatically improved outcomes for CML patients. PD-L1 testing can help predict which patients are likely to respond to immune checkpoint inhibitor therapy, which targets PD-L1 [47].

Therapy-related risk management

Biomarkers can help identify patients who are at increased risk of developing treatment-related toxicities, allowing for more personalized treatment regimens. Testing for certain genetic variants can help predict the risk of chemotherapy-induced peripheral neuropathy or other adverse effects. CYP2D6 genotype can help identify patients who may be at increased risk of developing toxicities from chemotherapy drugs like tamoxifen, which is used to treat breast cancer [48]. UGT1A1 is a gene that is involved in the metabolism of irinotecan, a chemotherapy drug used to treat several types of cancer and drug toxicity can be assessed [49].

Therapy monitoring

Biomarkers can be used to monitor the response to therapy and guide treatment decisions. Imaging biomarkers such as PET scans or MRIs can be used to assess the response of tumors to treatment, while blood-based biomarkers such as circulating tumor DNA (ctDNA) can provide early indications of treatment efficacy or resistance [50]. An integrated approach using PET/CT and PET/MRI as imaging biomarkers can be useful for the therapy endpoint selection, standard tool as imaging biomarkers reduce diagnostic variability [51].

Post-treatment monitoring

Biomarkers can be used to monitor patients for cancer recurrence or the development of secondary cancers. For example, measuring serum levels of certain proteins, such as CA-125 in ovarian cancer, can help detect cancer recurrence at an early stage and guide further treatment [52]. BNP and N-terminal proBNP is used in the clinical decision making treatment paediatrics with pulmonary hypertension. Quantification of HCV-RNA may serve as guide for monitoring hepatitis-C treatment. Similarly, PSA used for prostate cancer, HIV-RNA for antiretroviral therapy monitoring, prothrombin time is useful in follow-up after warfarin treatment [53]. Mycobacterium tuberculosis specific $CA4^{+}$ T cells can be used for post-treatment monitoring [54].

Challenges and limitations of PM in oncology

PM in oncology involves using a patient's genetic information to determine the most effective treatment for their cancer. While this approach has shown promise, some challenges and limitations need to be addressed. These challenges include data analysis, tumor heterogeneity, and clinical trial design, while limitations include cost, accessibility, ethical concerns, resistance to targeted therapies, etc. are depicted in Fig. 7.

The use of biomarker-based PM has the potential to revolutionize healthcare by improving the accuracy of diagnosis, the effectiveness of treatment, and ultimately patient outcomes. However, there are also potential consequences associated with the use of biomarkers in PM.

Complexity of tumor biology and heterogeneity

Tumor biology is a complex and heterogeneous process that involves numerous genetic and epigenetic alterations. Tumors can contain multiple subclones with different genetic mutations or other biomarkers. This means that different parts of the same tumor can have different molecular characteristics [55, 56]. Even tumors of the same type can have different molecular characteristics, making it difficult to identify a single biomarker that can be used to guide treatment decisions for all patients. Tumor heterogeneity has been recognized as a major contributor to the complexity of tumor biology. Tumor heterogeneity can occur both

Fig. 7 Challenges and Limitations in PM in Oncology

spatially and temporally, resulting in subpopulations of cells with distinct phenotypic and genotypic characteristics. This heterogeneity poses significant challenges to the diagnosis, prognosis, and treatment of cancer. Tumors can evolve, leading to changes in molecular characteristics and the emergence of new subclones. This can make it challenging to determine the most appropriate treatment for a patient based on a single biomarker [57]. Tumors can develop complex signaling pathways that interact with each other, making it difficult to identify a single target for therapy [58]. Not all tumors have biomarkers that are robust and reliable predictors of response to therapy. Some biomarkers may have limited sensitivity or specificity, leading to false positives or false negatives [59].

Limited availability of biomarkers

The limited availability of biomarkers is a major challenge in the field of PM. Biomarkers are molecular or cellular characteristics that can be used to identify a disease or its progression and can also be used to predict the response to therapy. However, the identification and validation of biomarkers is often a lengthy and expensive process, and many potential biomarkers fail to make it to the clinical setting due to limited availability [60]. The lack of biomarkers also limits the ability to personalized treatment for patients. Without reliable biomarkers, clinicians may have to rely on a trial-and-error approach to treatment, leading to delays in effective therapy and unnecessary side effects from ineffective treatments [61]. To address

this issue, researchers are exploring new methods for identifying biomarkers, such as the use of artificial intelligence and machine learning algorithms. These techniques can analyze large amounts of data and identify patterns that may not be apparent to the human eye, leading to the discovery of new biomarkers. Along with the limited availability of biomarkers, limited sensitivity and specificity, the need for specialized tools and techniques, cost and validation of the method parameters may pose the challenges in the clinical use of biomarkers [62].

High cost of targeted therapies

Targeted therapies have revolutionized cancer treatment by selectively targeting cancer cells and minimizing damage to healthy cells. However, these therapies are often associated with high costs, which can limit access for patients. The high cost of targeted therapies is due to a variety of factors, including the development and manufacturing process, the cost of clinical trials, and the exclusivity granted by patents. In addition to limiting patient access, the high cost of targeted therapies also puts a strain on healthcare systems and insurance providers. This can lead to difficult decisions about which treatments to cover and which patients to prioritize for treatment. To address this issue, researchers and policymakers are exploring new approaches to drug pricing and reimbursement, such as value-based pricing and outcome-based contracts [63].

Resistance to targeted therapies

The development of resistance in cancer tissues is a chief issue in the use of targeted cancer therapies. Resistance can arise from a variety of mechanisms, including genetic mutations, activation of alternative signaling pathways, and changes in the tumor microenvironment [64]. Research has shown that the development of resistance to targeted therapies can be delayed or prevented by combining targeted therapies with other treatment modalities, such as chemotherapy or immunotherapy. Additionally, the use of combination therapies that target multiple pathways involved in tumor growth and survival may reduce the likelihood of resistance development. Another approach to overcoming resistance to targeted therapies is the use of PM. By identifying specific molecular alterations in a patient's tumor, clinicians can tailor treatment to target those specific alterations, potentially increasing the effectiveness of therapy and reducing the likelihood of resistance [65].

Ethical and social issues

Biomarkers have revolutionized cancer treatment, allowing for more personalized and effective therapies. However, the development and use of targeted therapies also raise ethical and social issues that need to be addressed. One of the major issues is the high cost of biomarker testing and targeted therapies, which can limit access for patients who cannot afford them. Additionally, the use of targeted therapies can raise questions about the allocation of healthcare resources and the prioritization of certain patients over others in terms of receiving these treatments. Another ethical issue is the potential for targeted therapies to exacerbate existing health disparities, as certain populations may not have access to the same level of care or may not be included in clinical trials. Additionally, there are concerns about the potential for genetic discrimination, as the use of targeted therapies may reveal information about a patient's genetic makeup that could be used against them in areas such as employment or insurance [66].

Risk of misinterpretation

Biomarkers are complex indicators of disease, and their interpretation requires a deep understanding of the underlying biology and context of the patient. Misinterpretation of biomarker results can lead to inaccurate diagnoses, ineffective treatments, and unnecessary interventions. Biomarkers can give false positive or false negative results due to limited biomarker specificity, tumor heterogenicity or lack of standardization methods. Overreliance on the biomarkers leads missing important clinical information during treatment [67].

Conclusion and future perspectives

Targeted therapies are transforming cancer treatment, but there is more work ahead. PM needs better clinical guidelines, trials and biomarkers to enhance patient outcomes, demanding new practices and tools. Biomarkers improve treatment by matching patients' right therapy, saving costs. PM fight drug resistance through new targets and tailored treatments based on tumor characteristics, boosting outcomes.

In the future, we aim to improve biomarkers, discover new targets and explore therapies to combat resistance in cancer treatment. Challenges include high cost and ethical concerns. We need more sensitive diagnostic tools for limited biomarker quantities in the body fluids. Collaboration among researchers, clinicians, and policymakers is essential. Genomic sequencing enables personalized cancer treatment, and artificial intelligence helps to analyze vast data. Ongoing research is vital to find biomarkers, genetic drivers and affordable targeted treatment for wider patient population.

Abbreviations

BNP	B-type natriuretic peptide
BPH	Benign prostatic hyperplasia
BRCA1/2	Breast cancer type ½
BRAF	Raf murine sarcoma viral oncogene homolog B
CA-125	Cancer antigen 125
CEA	Carcinoembryonic antigen
CML	Chronic myelogenous leukemia
CRP	C-reactive protein
dTMP	Deoxythymidine monophosphate
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
IMP	Inosine monophosphate
KRAS	Kirsten rat sarcoma viral oncogene homolog
MAPK	Mitogen-activated protein kinase
MLH1	MutL protein homolog 1
MRI	Magnetic resonance imaging
MSH2/6	MutS homolog 2/6
MSI	Microsatellite instability
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PARP	Poly ADP-ribose polymerase
PM	Personalized medicine
PMS1/2	PMS1 homolog 2
PR	Progesterone receptor
PSA	Prostate-specific antigen
TK	Tyrosine kinase

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References

1. Gambardella V, Tarazona N, Cejalvo JM et al (2020) Personalized medicine: recent progress in cancer therapy. Cancers (Basel) 12:1009. https://doi.org/10.3390/cancers12041009
2. Personalized Medicine. In: Natl. Hum. Genome Res. Inst. https://www.genome.gov/genetics-glossary/Personalized-Medicine. Accessed 7 Nov 2023
3. Xu J, Yang P, Xue S et al (2019) Translating cancer genomics into precision medicine with artificial intelligence: applications, challenges and future perspectives. Hum Genet 138:109–124. https://doi.org/10.1007/s00439-019-01970-5
4. Vranic S, Gatalica Z (2021) The role of pathology in the era of personalized (precision) medicine: a brief review. Acta Med Acad 50:47. https://doi.org/10.5644/ama2006-124.325
5. Yersal O, Barutca S (2014) Biological subtypes of breast cancer: prognostic and therapeutic implications. World J Clin Oncol 5:412. https://doi.org/10.5306/wjco.v5.i3.412
6. Marrugo-Ramírez J, Mir M, Samitier J (2018) Blood-based cancer biomarkers in liquid biopsy: a promising non-invasive alternative to tissue biopsy. Int J Mol Sci 19:2877. https://doi.org/10.3390/ijms19102877
7. Biomarker Testing for Cancer Treatment. In: Natl. Cancer Inst. https://www.cancer.gov/about-cancer/treatment/types/biomarker-testing-cancer-treatment. Accessed 16 Mar 2023
8. Ferro M, La Civita E, Liotti A et al (2021) Liquid biopsy biomarkers in urine: a route towards molecular diagnosis and personalized medicine of bladder cancer. J Pers Med 11:237. https://doi.org/10.3390/jpm11030237
9. Tainsky MA (2009) Genomic and proteomic biomarkers for cancer: a multitude of opportunities. Biochim Biophys Acta Rev Cancer 1796:176–193. https://doi.org/10.1016/j.bbcan.2009.04.004
10. Genes and Cancer. In: Am. Cancer Soc. Inc. https://www.cancer.org/healthy/cancer-causes/genetics/genes-and-cancer/oncogenes-tumor-suppressor-genes.html. Accessed 7 Nov 2023
11. Joyce C, Rayi A, Kasi A (2023) Tumor-suppressor genes. In: StatPearls Publ. https://www.ncbi.nlm.nih.gov/books/NBK532243/. Accessed 5 Aug 2023
12. Hause RJ, Pritchard CC, Shendure J, Salipante SJ (2016) Classification and characterization of microsatellite instability across 18 cancer types. Nat Med 22:1342–1350. https://doi.org/10.1038/nm.4191
13. Li K, Luo H, Huang L et al (2020) Microsatellite instability: a review of what the oncologist should know. Cancer Cell Int 20:16. https://doi.org/10.1186/s12935-019-1091-8
14. Talking Glossary of Genomic and Genetic Terms. In: Natl. Hum. Genome Res. Inst. https://www.genome.gov/genetics-glossary. Accessed 7 Nov 2023
15. Kim M, Costello J (2017) DNA methylation: an epigenetic mark of cellular memory. Exp Mol Med 49:e322–e322. https://doi.org/10.1038/emm.2017.10
16. Ramazi S, Allahverdi A, Zahiri J (2020) Evaluation of post-translational modifications in histone proteins: a review on histone modification defects in developmental and neurological disorders. J Biosci 45:135. https://doi.org/10.1007/s12038-020-00099-2
17. Millán-Zambrano G, Burton A, Bannister AJ, Schneider R (2022) Histone post-translational modifications: cause and consequence of genome function. Nat Rev Genet 23:563–580. https://doi.org/10.1038/s41576-022-00468-7
18. Landegren U, Hammond M (2021) Cancer diagnostics based on plasma protein biomarkers: hard times but great expectations. Mol Oncol 15:1715–1726. https://doi.org/10.1002/1878-0261.12809
19. Mussap M, Zaffanello M, Fanos V (2018) Metabolomics: a challenge for detecting and monitoring inborn errors of metabolism. Ann Transl Med 6:338–338. https://doi.org/10.21037/atm.2018.09.18
20. Schmidt DR, Patel R, Kirsch DG et al (2021) Metabolomics in cancer research and emerging applications in clinical oncology. CA Cancer J Clin 71:333–358. https://doi.org/10.3322/caac.21670
21. Lieu EL, Nguyen T, Rhyne S, Kim J (2020) Amino acids in cancer. Exp Mol Med 52:15–30. https://doi.org/10.1038/s12276-020-0375-3
22. Fu Y, Zou T, Shen X et al (2021) Lipid metabolism in cancer progression and therapeutic strategies. MedComm 2:27–59. https://doi.org/10.1002/mco2.27
23. Hossain F, Andreana PR (2019) Developments in carbohydrate-based cancer therapeutics. Pharmaceuticals 12:84. https://doi.org/10.3390/ph12020084
24. Yang X, Kui L, Tang M et al (2020) High-throughput transcriptome profiling in drug and biomarker discovery. Front Genet. https://doi.org/10.3389/fgene.2020.00019
25. Vieira AF, Schmitt F (2018) An update on breast cancer multigene prognostic tests: emergent clinical biomarkers. Front Med. https://doi.org/10.3389/fmed.2018.00248

26. Herlemann A, Huang H-C, Alam R et al (2020) Decipher identifies men with otherwise clinically favorable-intermediate risk disease who may not be good candidates for active surveillance. Prostate Cancer Prostatic Dis 23:136–143. https://doi.org/10.1038/s41391-019-0167-9
27. Zhang G, Pian C, Chen Z et al (2018) Identification of cancer-related miRNA-lncRNA biomarkers using a basic miRNA-lncRNA network. PLoS ONE 13:e0196681. https://doi.org/10.1371/journal.pone.0196681
28. Anastasiadou E, Jacob LS, Slack FJ (2018) Non-coding RNA networks in cancer. Nat Rev Cancer 18:5–18. https://doi.org/10.1038/nrc.2017.99
29. deSouza NM, Achten E, Alberich-Bayarri A et al (2019) Validated imaging biomarkers as decision-making tools in clinical trials and routine practice: current status and recommendations from the EIBALL* subcommittee of the European Society of Radiology (ESR). Insights Imaging 10:87. https://doi.org/10.1186/s13244-019-0764-0
30. Sinigaglia M, Assi T, Besson FL et al (2019) Imaging-guided precision medicine in glioblastoma patients treated with immune checkpoint modulators: research trend and future directions in the field of imaging biomarkers and artificial intelligence. EJNMMI Res 9:78. https://doi.org/10.1186/s13550-019-0542-5
31. Mikdadi D, O'Connell KA, Meacham PJ et al (2022) Applications of artificial intelligence (AI) in ovarian cancer, pancreatic cancer, and image biomarker discovery. Cancer Biomark 33:173–184. https://doi.org/10.3233/CBM-210301
32. Eiger D, Agostinetto E, Saúde-Conde R, de Azambuja E (2021) The exciting new field of HER2-low breast cancer treatment. Cancers (Basel) 13:1015. https://doi.org/10.3390/cancers13051015
33. Schlam I, Swain SM (2021) HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. npj Breast Cancer 7:56. https://doi.org/10.1038/s41523-021-00265-1
34. O'Leary C, Gasper H, Sahin KB et al (2020) Epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC). Pharmaceuticals 13:273. https://doi.org/10.3390/ph13100273
35. Yan N, Guo S, Zhang H et al (2022) BRAF-mutated non-small cell lung cancer: current treatment status and future perspective. Front Oncol. https://doi.org/10.3389/fonc.2022.863043
36. Angerilli V, Sabella G, Centonze G et al (2022) BRAF-mutated colorectal adenocarcinomas: pathological heterogeneity and clinical implications. Crit Rev Oncol Hematol 172:103647. https://doi.org/10.1016/j.critrevonc.2022.103647
37. Tanda ET, Vanni I, Boutros A et al (2020) Current state of target treatment in BRAF mutated melanoma. Front Mol Biosci. https://doi.org/10.3389/fmolb.2020.00154
38. Gonçalves D, Pires AS, Marques IA et al (2022) An overview on radiation sensitivity in hereditary breast and ovarian cancer syndrome. Cancers (Basel) 14:3254. https://doi.org/10.3390/cancers14133254
39. Huber-Keener KJ (2022) Cancer genetics and breast cancer. Best Pract Res Clin Obstet Gynaecol 82:3–11. https://doi.org/10.1016/j.bpobgyn.2022.01.007
40. Dean L, Kane M (2020) Cetuximab therapy and RAS and BRAF genotype. In: Pratt V, Scott S, Pirmohamed M (eds) Medical genetics summaries. National Center for Biotechnology Information (US), Bethesda
41. Holdenrieder S, Ungerer V, Oberhofer A, Bronkhorst AJ (2022) Pan-cancer screening by circulating tumor DNA (ctDNA): recent breakthroughs and chronic pitfalls. J Lab Med 46:247–253. https://doi.org/10.1515/labmed-2022-0029
42. de Kock R, van den Borne B, El S et al (2021) Circulating biomarkers for monitoring therapy response and detection of disease progression in lung cancer patients. Cancer Treat Res Commun 28:100410. https://doi.org/10.1016/j.ctarc.2021.100410
43. Vaidyanathan K, Vasudevan DM (2012) Organ specific tumor markers: what's new? Indian J Clin Biochem 27:110–120. https://doi.org/10.1007/s12291-011-0173-8
44. Vandghanooni S, Sanaat Z, Farahzadi R et al (2021) Recent progress in the development of aptasensors for cancer diagnosis: focusing on aptamers against cancer biomarkers. Microchem J 170:106640. https://doi.org/10.1016/j.microc.2021.106640
45. Hill A, Gupta R, Zhao D et al (2019) Targeted therapies in non-small-cell lung cancer. In: Precision medicine in cancer therapy, pp 3–43
46. Ziaran S, Harsanyi S, Bevizova K et al (2020) Expression of E-cadherin, Ki-67, and p53 in urinary bladder cancer in relation to progression, survival, and recurrence. Eur J Histochem. https://doi.org/10.4081/ejh.2020.3098
47. Baliu-Piqué M, Pandiella A, Ocana A (2020) Breast cancer heterogeneity and response to novel therapeutics. Cancers (Basel) 12:3271. https://doi.org/10.3390/cancers12113271
48. Rodrigues R, Duarte D, Vale N (2022) Drug repurposing in cancer therapy: influence of patient's genetic background in breast cancer treatment. Int J Mol Sci 23:4280. https://doi.org/10.3390/ijms23084280
49. Nelson RS, Seligson ND, Bottiglieri S et al (2021) UGT1A1 guided cancer therapy: review of the evidence and considerations for clinical implementation. Cancers (Basel) 13:1566. https://doi.org/10.3390/cancers13071566
50. Han X, Wang J, Sun Y (2017) Circulating tumor DNA as biomarkers for cancer detection. Genom Proteom Bioinform 15:59–72. https://doi.org/10.1016/j.gpb.2016.12.004
51. Sorace AG, Elkassem AA, Galgano SJ et al (2020) Imaging for response assessment in cancer clinical trials. Semin Nucl Med 50:488–504. https://doi.org/10.1053/j.semnuclmed.2020.05.001
52. Scholler N, Urban N (2007) CA125 in ovarian cancer. Biomark Med 1:513–523. https://doi.org/10.2217/17520363.1.4.513
53. Adeniyi O, Aguel F, Agyeman A et al (2021) BEST (Biomarkers, EndpointS, and other Tools) resource. In: Food drug adm. (US); Bethesda Natl. Institutes Heal. https://www.ncbi.nlm.nih.gov/books/NBK338449/. Accessed 22 Sep 2023
54. Yong YK, Tan HY, Saeidi A et al (2019) Immune biomarkers for diagnosis and treatment monitoring of tuberculosis: current developments and future prospects. Front Microbiol. https://doi.org/10.3389/fmicb.2019.02789
55. Karthik G-M, Rantalainen M, Stålhammar G et al (2017) Intra-tumor heterogeneity in breast cancer has limited impact on transcriptomic-based molecular profiling. BMC Cancer 17:802. https://doi.org/10.1186/s12885-017-3815-2
56. Dentro SC, Leshchiner I, Haase K et al (2021) Characterizing genetic intra-tumor heterogeneity across 2,658 human cancer genomes. Cell 184:2239-2254.e39. https://doi.org/10.1016/j.cell.2021.03.009
57. Brady SW, McQuerry JA, Qiao Y et al (2017) Combating subclonal evolution of resistant cancer phenotypes. Nat Commun 8:1231. https://doi.org/10.1038/s41467-017-01174-3
58. Hon KW, Zainal Abidin SA, Othman I, Naidu R (2021) The crosstalk between signaling pathways and cancer metabolism in colorectal cancer. Front Pharmacol. https://doi.org/10.3389/fphar.2021.768861
59. Nabavizadeh N (2022) The clinical and economic benefits associated with novel multi-cancer early detection tests: conference highlights from the 2022 ISPOR annual meeting. Am J Manag Care 28:S123–S132. https://doi.org/10.37765/ajmc.2022.89216
60. Castelli FA, Rosati G, Moguet C et al (2022) Metabolomics for personalized medicine: the input of analytical chemistry from biomarker discovery to point-of-care tests. Anal Bioanal Chem 414:759–789. https://doi.org/10.1007/s00216-021-03586-z
61. Pitzalis C, Choy EHS, Buch MH (2020) Transforming clinical trials in rheumatology: towards patient-centric precision medicine. Nat Rev Rheumatol 16:590–599. https://doi.org/10.1038/s41584-020-0491-4
62. Davenport T, Kalakota R (2019) The potential for artificial intelligence in healthcare. Futur Healthc J 6:94–98. https://doi.org/10.7861/futurehosp.6-2-94
63. Garland M, Yim JJ, Bogyo M (2016) A bright future for precision medicine: advances in fluorescent chemical probe design and their clinical application. Cell Chem Biol 23:122–136. https://doi.org/10.1016/j.chembiol.2015.12.003
64. Smith LK, Sheppard KE, McArthur GA (2021) Is resistance to targeted therapy in cancer inevitable? Cancer Cell 39:1047–1049. https://doi.org/10.1016/j.ccell.2021.07.013
65. Siemer S, Bauer TA, Scholz P et al (2021) Targeting cancer chemotherapy resistance by precision medicine-driven nanoparticle-formulated cisplatin. ACS Nano 15:18541–18556. https://doi.org/10.1021/acsnano.1c08632
66. Lehmann LS, Snyder Sulmasy L, Burke W et al (2022) Ethical considerations in precision medicine and genetic testing in internal medicine

practice: a position paper from the American College of Physicians. Ann Intern Med 175:1322–1323. https://doi.org/10.7326/M22-0743
67. Schuetz P, Aujesky D, Müller C, Müller B (2015) Biomarker-guided personalised emergency medicine for all: hope for another hype? Swiss Med Wkly. https://doi.org/10.4414/smw.2015.14079

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